REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Applicants amend claims 8, 12 and 16, and add new claims 29 and 30. Support for newly introduced claims 29 and 30 exists throughout the originally filed specification, for example, at pages 1, lines 20-26, Table 1, Example 1 and originally filed claims 1 and 3. The amendments and new claims introduce no new matter.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Applicants thank the Examiner for entering the Reply and amendments of October 27, 2008. After amending the claims as set forth herein, claims 3-8, 12, 16, 20-30 are pending in this application, although claims 3-7 are withdrawn. In the most recent Office Action, the Examiner examined claims 8, 12, 16 and 20-28 on the merits.

The Examiner has rejected claims 8, 12, 16 and 20-28 as obvious over EP 0115627 ("APC"), U.S. Pat. No. 5,759,565 ("Azria") and U.S. Pat. No. 5,026,825 ("Grebow"). In the recent Office Action, the Examiner states that Azria taught that in a relevant nasal composition chlorobutanol "suffers some drawbacks when used at concentrations above 0.6%" but does not use or teach chlorobutanol "at ranges instantly claimed" i.e., between about 0.25% and about 0.4% weight/weight. Office Action, page 4. The Examiner goes on to state that "Applicants have focused on the A[z]ria et al article throughout the prosecution history, and soley because of the teaching of chlorobutanol concentrations above 0.6% have undesired effects." Office Action, page 7. The Examiner appears to assume that Azria teaches that "the concentration of chlorobutanol should be kept below 0.6% to prevent or minimize the destructive properties of the rubber stopper." Office Action, page 8. The Examiner then asserts that "the teaching of an upper limit on a given component is not teaching away from the use of chlorobutanol in its entirety." *Id.*

Applicants respectfully submit that they have "focused" on Azria precisely because this reference squarely and expressly teaches away from using chlorobutanol at all, in any amount, i.e., in its entirety, as a preservative in an aqueous solution of calcitonin. *See* M.P.E.P. 2144.05 (stating that obviousness may "be rebutted by showing that the art, in any material respect, teaches away from the claimed invention.").

To clarify, Azria states the following:

> Very many well-known preserving agents present themselves for possible use in calcitonin pharmaceutical compositions. **However experiment has shown that not all are suitable for practical use in relation to a calcitonin nasal spray.** Thus **chlorbutanol at 0.6% in calcitonin nasal pharmaceutical compositions showed insufficient activity against the test fungus *Pen. steckii*, more than 3 days being required to reduce the cell count to less than 0.1%.** Moreover, **chlorbutanol was found to attack rubber stoppers and other joints used in nasal spray applicators between the spray pump and a bottle.**
>
> **Chlorbutanol additionally caused at 0.6% more than 50% inhibition of the ciliary beating frequency of rat trachea within 20 minutes according to the microphoto-oscillographic method of L. Chevance et al, Acta Otolaryng. 70, 16:28 (1970). These are just some of the disadvantageous effects that can be encountered.**
>
> **In accordance with the present invention it has now been surprisingly found that pharmaceutical compositions can be obtained comprising a calcitonin as active ingredient which meet the high standards of stability and tolerability required for nasal application** and which are, for example, eminently suitable for use in multiple dose nasal spray applicators, i.e. applicators capable of delivering a series of individual dosages over e.g. period of several days or weeks, **by the use of benzalkonium chloride as a co-ingredient and preserving agent.** ...

Azria, col. 4, lines 35-67. Applicants submit, based on the above-quoted teachings, it would have been abundantly clear to anyone skilled in the art that Azria expressly taught away from using chlorobutanol as a preservative in a calcitonin pharmaceutical composition in any amount.

As noted above, Azria stated that experiment had shown that not all well-known preserving agents were suitable for practical use in relation to a calcitonin nasal spray. Azria

then expressly talked about the unsuitability of chlorbutanol in particular when it stated: "chlorbutanol at 0.6% in calcitonin nasal pharmaceutical compositions showed insufficient activity against the test fungus *Pen. Steckii* ...." Thus, Azria taught that a concentration of chlorbutanol as high as 0.6% was insufficiently active against a well-known test microorganism. *See* Declaration of Henry R. Costantino dated August 24, 2007, pages 2-3, ¶8. Likewise, as noted in Dr. Costantino's Declaration, those skilled in the would have understood that chlorobutanol at lower concentrations would be even less effective in killing relevant microorganisms. *Id.* at page 3, ¶9, ¶10. In other words, Azria taught those skilled in the art that chlorbutanol was ineffective as a preservative at concentrations of 0.6% or less. As such, this disclosure taught away from using 0.6% or less of chlorobutanol—Azria taught that such an amount rendered this preservative ineffective for its intended purpose.

As it turns out, this particular teaching of Azria was actually relatively consistent with teachings in the earlier references of APC and Grebow regarding appropriate amounts of preservative to use. Of course, because the two references existed earlier in time, the scientists of APC (published in 1987) and Grebow (issued in 1991) did not have the benefit of the experimental data available to Azria (issued in 1998). That said, both APC and Grebow taught using chlorobutanol at a concentration of 0.5 – 1.0 w/v%, i.e., corresponding in significant part to amounts greater than 0.6 w/w%.

Azria also taught that "chlorbutanol was found to attack rubber stoppers and other joints used in nasal spray applicators between the spray pump and a bottle." Thus, this reference taught that chlorobutanol, as a general matter, was further unsuitable because it caused damage to different components of the nasal spray applicators. Unlike in other sentences highlighted above, Azria did not expressly refer to an amount of chlorobutanol that might cause such damage. As such, those skilled in the art would have read this sentence to mean that any amount could cause damage.

In any event, Azria taught that "[c]hlorbutanol additionally caused at 0.6% more than 50% inhibition of the ciliary beating frequency of rat trachea within 20 minutes," as shown in previous work of others. In other words, Azria indicated that at a concentration of 0.6%, this preservative caused an unsuitable side effect in the trachea. Those skilled the art would have

understood that a side effect at one concentration (0.6%) would most likely be more severe at a higher concentration (i.e., greater than 0.6%). Thus, consistent with statements by the Examiner in this case, Azria clearly taught away from using chlorobutanol at a concentration of 0.6% or higher. *See* recent Office Action, page 4 (stating that "Azria teaches that concentration of chlorobutanol above 0.6% have undesired side effects.").

In sum, Azria taught those skilled in the art that they should not use chlorobutanol at concentrations of 0.6% or less because experimental data showed that this compound was ineffective for its intended purpose as a preservative at these concentrations. Azria also taught those skilled in the art that they should not use chlorobutanol at concentrations of 0.6% or higher because this compound caused undesirable side effects at these concentrations. Azria also stated that the above-mentioned problems with chlorobutanol "are just some of the disadvantageous effects that can be encountered."

For the above-mentioned reasons, one reading Azria would have had no reasonable expectation of success in using chlorobutanol at all, at any concentration, as a preservative in a calcitonin nasal spray. *See* M.P.E.P. 2143.02 (stating that reasonable expectation of success is required). Rather, as repeatedly stated throughout Azria, this reference taught those skilled in the art to use a different preservative, benzalkonium chloride, when preparing a calcitonin nasal formulation that could "meet the high standards of stability and tolerability required for nasal application." Azria, col. 2, lines 52-61.

In light of teachings in Azria, those skilled in the art would have under understood that Applicants' claimed compositions, especially in light of experimental data presented in Dr. Costantino's Declaration (*see, e.g.,* page 2, Table 1; page 3, ¶3), provided surprising results. Specifically, Applicants disclosed novel calcitonin compositions, where the compositions comprised chlorobutanol at a concentration less than 0.6% (e.g., 0.25%) that worked suitably well as a preservative. *See* Dr. Costantino's Declaration, page 2, ¶6.

All of Applicants' pending claims recite the transition language of "consisting of." As such, the recited compositions exclude benzalkonium chloride as preservative, i.e., the preservative taught in Azria. Thus, Azria cannot render Applicants' claims obvious, either

alone or in combination with any other cited reference. Likewise, APC and Grebow each required at least one additional component not present in Applicants' recited compositions. For example, APC required that "calcitonin is used in combination with a bile salt surface active agent as absorption promoter" (page 3, lines 11-17). In addition, Grebow required that Δ-aminolevulinic acid be present in calcitonin-containing pharmaceutical formulations (abstract; col. 1, lines 8-13). Thus, APC and/or Grebow, either alone or in combination with any cited reference, cannot render Applicants' claims obvious when none of these references taught or suggested a composition that excluded any additional components, such as benzalkonium chloride, a bile salt surface active agent and/or Δ-aminolevulinic acid.

As noted above, Azria became publicly available to those skilled in the art much later than either APC or Grebow. Both APC and Grebow disclosed a number of possible preservatives for use in calcitonin formulations, such as thimerosol (0.001 – 0.01 w/v%), chlorobutanol (0.5 – 1.0 w/v%) and phenethyl alcohol (0.25 – 0.75 w/v%). *See* APC, page 3, lines 40-55 (describing seven different preservatives); Grebow, col. 12, lines 1-13 (describing nine different preservatives). When trying to capture all possible preservatives generally, both references referred to a broad range of 0.001 – 2.0% w/v, where 0.001% captured the lowest range of thimerosol, for example. Regarding chlorobutanol in particular, however, APC and Grebow taught the use of this composition as a preservative, but at a concentration of 0.5 – 1.0 w/v%, i.e., higher than the range of concentrations of chlorobutanol recited in Applicants' claims.

The Examiner relies on Example 9 in Grebow (col. 13), and presumably Example 3 in APC (page 4), to assert that these references taught the use of chlorobutanol at a concentration as low as 0.1 w/v%. What the Examiner fails to acknowledge, however, is that these Examples presented formulations having at least two different preservatives, i.e., chlorobutanol at 0.1 w/v% and phenethyl alcohol at 0.2 w/v%. APC, page 4, lines 45-47; Grebow, col. 13, lines 14-15. Concentrations of both preservatives were lower than the otherwise presented ranges for these two preservatives. In other words, these references suggested that one needed less of any one preservative if the formulation also included a second preservative. Thus, those skilled in the art would not have read either APC or Grebow as teaching 0.1 w/v%—or any concentration of below 0.5% for that matter—of chlorobutanol

in a calcitonin formulation, when the formulation had chlorobutanol as the only listed preservative.

As mentioned above, Applicants' pending claims recite "consisting of." Thus, the recited compositions do not include phenethyl alcohol, i.e., the second preservative present in Example 3 of APC and Example 9 of Grebow. Those Examples would not have taught or suggested making a calcitonin formulation having 0.1% w/v chlorobutanol and lacking phenethyl alcohol. Rather, one reading these Examples would have been motivated to include another preservative, such as phenethyl alcohol, if using chlorobutanol at a concentration less than the taught range of 0.5 – 1.0% w/v.

Furthermore, both APC and Grebow wholly failed to address or even consider whether chlorobutanol was effective as a preservative at a concentration below 0.6%. As such, those skilled in the art would have relied on the later teaching in Azria, which provided specifics regarding chlorobutanol in this regard. One reading APC and/or Grebow, in combination with Azria, would have understood that chlorobutanol alone failed to work as a preservative at concentrations of 0.6% or less. Moreover, in light of Azria's teachings about the side effects of chlorobutanol at concentrations of 0.6% or greater (an issue also not addressed in APC or Grebow), those skilled in the art would have used different preservatives, such as those disclosed in APC and Grebow, but not chlorobutanol.

Lastly, regarding claims 20-28 directed to pharmaceutical devices, the Examiner contends that recited elements of these claims, such as spray pattern ellipticity ratio, spray pattern major and minor axis and droplet size, "are a function of the applicator and do not have patentable weight on the composition itself." Office Action, page 6. Applicants respectfully submit that the Examiner bears the burden of establishing a prima facie case that the recited devices, which combine the compositions at issue with actuators capable of producing certain recited spray features, would have been obvious. The Examiner fails to meet this burden by simply asserting the compositions are obvious. The Examiner cannot meet his burden regarding claims 20-28 without considering other elements in the claims, and/or without considering or mentioning whether any relevant prior reference teaches or suggests devices capable of producing such spray patterns.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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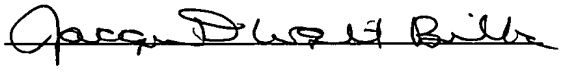
By 

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